COMPOSITION FOR CONTRACEPTION

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

[This] *This application is the parent of application Ser. No. 09/504,084, both filed Feb. 15, 2000, both of which are reissues of application Ser. No. 08/742,147, filed Oct. 31, 1996, now U.S. Pat. No. 5,824,667, which* is a continuation of the application Ser. No. 08/268,996 filed Jun. 30, 1994, now U.S. Pat. No. 5,583,129.

DESCRIPTION

This invention relates to the common use of estrogen and gestagens for the production of a combination preparation for oral contraception and a corresponding pack containing this combination preparation.

Combination preparations for oral contraception are already known, for example, Femovan® [DE-PS 2 546 062] or Marvelon® [DE-OS 2 361 120]. These preparations consist of 21 active ingredient-containing (estrogen/gestagen) dosage units and 7 active ingredient-free coated tablets (sugar pills; placebos). The dose to be administered daily is uniformly high in each case (so-called single-phase preparations) and produces the desired contraceptive effect in the entire intake period and in the intake pause or during the intake of the placebos. In most preparations, a 7-day interruption of the intake of active ingredient-containing dosage units was considered necessary until quite recently to trigger a reliable withdrawal bleeding and thus to achieve a satisfactory cycle control.

Other preparations, which exhibit more than 21 dosage units containing an estrogenic and progestational active ingredient, and in which the intake pause is partially (Ijzerman, Pasquale) or completely (Kuhl) bridged over by estrogen-containing dosage units. In this case, it is possible that the synthetic estrogen ethinylestradiol otherwise contained in oral contraceptives is replaced partially or completely by a conjugated estrogen, preferably estradiol.

A combination preparation for substitution therapy and contraception for females before menopause (approximately starting from the 40th year of life) is known from EP-A-0 253 607. This combination preparation contains an estrogen from the group

17β-Estradiol,
ethinylestradiol and
mestranol

as well as a gestagen from the group

levonorgestrel,
gestodene,
desogestrel,
3-ketodesogestrel and
norethindrone.

A thus selected composition is to offset hormonal irregularities in the transition phase of premenopause and to help alleviate the symptoms caused by the hormonal changeover of the female organism in this phase. Such a composition simultaneously assures a premenopausal female the contraceptive protection still necessary at this age.

The development of new oral contraceptives for females of reproductive age before premenopause was characterized during the last twenty years above all by the reduction of the estrogen and gestagen dosages.

The reduction of the daily hormone dose was connected with the expectation to minimize the frequency of undesired side effects. Epidemiological data collected in the meantime confirm the desired trend toward better compatibility of lower-dosed preparations relative to cardiovascular complications [(1.) Thorogood, M., Oral Contraceptives and Cardiovascular Disease: An Epidemiologic Overview; Pharmaceoepidemiology and Drug Safety, Vol. 2: 3–16 (1993); (2.) Gerstman, B. B.; Piper, J. M.; Tomita, D. K.; Ferguson, W. J.; Stadel., B. V.; Lundin, F. E.; Oral Contraceptive Estrogen Dose and the Risk of Deep Venous Thromboembolic Disease, Am. J. E., Vol. 133, No. 1, 32–36 (1991); (3.) Lidegaard, O., Oral contraception and risk of a cerebral thromboembolic attack: results of a case-control study; BMJ Vol. 306, 956–63 (1993); (4.) Vessey, M.; Mant, D.; Smith, A.; Yeates, D.; Oral contraceptives and venous thromboembolism: findings in a large prospective study; BMJ, Vol. 292, (1986); (5.) Mishell, D. R., Oral Contraception: Past, Present and Future Perspectives; Int. J. Fertil., 36 Suppl., 7–18 (1991)].

It is assumed that a correlation exists above all between the level of the estrogen dose and the incidence of cardiovascular diseases. But the maintenance of the contraceptive effectiveness stands in the way of an extreme reduction of the daily estrogen dose. Although the ovulation-inhibiting effect of the low-dosed oral contraceptives is caused mainly by the gestagenic component, the estrogenic component also makes a significant contribution to the central inhibition action and to the ovarian suppression (ovulation inhibition). Moreover, the daily estrogen dose must not fall below the minimum dose ranges, so that a satisfactory cycle control can be assured (Der Frauenarzt [The Gynecologist]; 34, 7: 793 (1993)].

The lowest estrogen dose contained in an oral contraceptive on the market at this time is 20 μg of ethinylestradiol, combined with 150 μg of desogestrel (Mercilon). Although the cycle control of this preparation is, as expected, somewhat poorer in comparison to preparations with a higher estrogen dose, the high acceptance rate of Mercilon indicates a small clinical relevance of this drawback. But the observation, made identically in several studies, of a lesser ovarial suppression of the preparation containing 20 μg of ethinylestradiol represents a clinically important problem. Obviously with this very low estrogen dose, in the case of many females, the maturation of follicles, which could be detected with ultrasonic studies or hormonal studies, results [(6.) Lunell, N. O.; Carström, K.; Zador, G.; Ovulation inhibition with a combined oral contraceptive containing 20 μg of ethinylestradiol and 250 μg of levonorgestrel; Acta. Obstet. Gynecol. Scand. Suppl. 88: 17–21 (1979); (7.) Mall-Haefeli, M.; Werner-Zodrow, I.; Huber, P. R.; Klinische Erfahrungen mit Mercilon und Marvelon unter besonderer Berücksichtigung der Ovar-Funktion [Clinical Experience with Mercilon and Marvelon under special consideration of the ovary function]; Geburtsh. und Frauenheilk. [Obstetrics and Gynecology] 51, 35–38, Georg Thieme Verlag, Stuttgart-New York (1991); (8.) Strobel, E., Behandlung mit oralen Kontrazeptiva [Treatment with Oral Contraceptives]; Fortschr. Med. Vol. 110, No. 20 (1992); (9.) Letter to Editor, Contraception 45: 519–521 (1992); (10.) Teichmann, A. T.; Brill, K.; Can Dose Reduction of Ethinylestradiol in OCs Jeopardize Ovarian Suppression and Cycle Control? Abstract Book, VIIIth World Congress on Human Reproduction, Bali, Indonesia (1993)].

The hormone determinations performed showed that functional granulosa cells that secrete 17β-estradiol are involved. Each intake error in the case of females with clear ovarian activity, thus with follicular maturations, can result in a quick increase of gonadotropin production. The require-